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STATE-OF-THE-ART PAPER

Adiponectin and Cardiovascular Disease

Response to Therapeutic Interventions

Seung Hwan Han, MD, PHD,* Michael J. Quon, MD, PHD,† Jeong-a Kim, PHD,†
Kwang Kon Koh, MD, PHD, FACC*

Incheon, Korea; and Bethesda, Maryland

Adiponectin is a protein secreted specifically by adipose cells that may couple regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance. Obesity-related disorders including the metabolic syndrome, diabetes, atherosclerosis, hypertension, and coronary artery disease are associated with decreased plasma levels of adiponectin, insulin resistance, and endothelial dysfunction. Adiponectin has insulin-sensitizing effects as well as antiatherogenic properties. Lifestyle modifications and some drug therapies to treat atherosclerosis, hypertension, and coronary heart disease have important effects to simultaneously increase adiponectin levels, decrease insulin resistance, and improve endothelial dysfunction. In this review, we discuss insights into the relationships between adiponectin levels, insulin resistance, and endothelial dysfunction that are derived from various therapeutic interventions. The effects of lifestyle modifications and cardiovascular drugs on adiponectin levels and insulin resistance suggest plausible mechanisms that may be important for treating atherosclerosis and coronary heart disease. (J Am Coll Cardiol 2007;49:531–8) © 2007 by the American College of Cardiology Foundation

Elevated levels of free fatty acids associated with insulin resistance, obesity, diabetes, and the metabolic syndrome cause endothelial dysfunction by activating innate immune inflammatory pathways upstream of nuclear transcription factor kappa B (NF-κB). Thus, inflammation contributes to endothelial dysfunction (1,2). The resultant decrease in nitric oxide (NO) bioactivity is important in the initiation, progression, and clinical expression of atherosclerosis. Insulin resistance (1), systemic hypertension, and hypercholesterolemia (2) all contribute independently to endothelial dysfunction accompanied by inflammation in the vessel wall, which promotes development of atherosclerosis and coronary heart disease.

Endothelial dysfunction is characterized by impaired NO release from endothelium and decreased blood flow to insulin target tissues (3). This results in impaired delivery of substrate and hormone to skeletal muscle, which contributes to insulin resistance. The pathogenic relationships among obesity, the metabolic syndrome, and its cardiovascular complications are well established. However, mechanisms by which excess adiposity causes both insulin resistance and vascular dysfunction are not well understood. Increasing attention has been paid to the direct vascular effects of plasma proteins that originate from adipose tissue, especially adiponectin. Decreased plasma adiponectin levels are observed in patients with diabetes, metabolic syndrome, and coronary artery disease (4,5), and this may play a key role in the development of insulin resistance. Although the mechanisms underlying anti-inflammatory properties of adiponectin are not well understood (6), adiponectin's anti-inflammatory and antiatherogenic properties may be related, in part, to its ability to stimulate production of NO from vascular endothelium (7).

In this review, we discuss the antiatherogenic effects of adiponectin and its properties to improve and mimic metabolic and vascular actions of insulin. Particular emphasis is given to insights derived from therapeutic interventions with diet, exercise, cardiovascular drugs, insulin sensitizers, and combination therapies that simultaneously raise adiponectin levels and improve insulin sensitivity and endothelial function.

Biology, Regulation, and Metabolism of Adiponectin

The adipocyte is an active endocrine secretory cell releasing free fatty acids and producing several cytokines including tumor necrosis factor (TNF)-α, interleukins (ILs), leptin, and adiponectin (6). Adiponectin is the most abundant adipokine secreted by adipose cells that may couple regulation of insulin sensitivity with energy metabolism. Adiponectin is a 30-kDa protein that consists of an N-terminal collagenous domain and a C-terminal globular domain. Under normal conditions, the adiponectin gene (*AMP1*)

From the *Division of Cardiology, Gil Heart Center, Gachon Medical School, Incheon, Korea; and †Diabetes Unit, Laboratory of Clinical Investigation, NCCAM, NIH, Bethesda, Maryland.

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Abbreviations and Acronyms

AMP = adenosine monophosphate
CRP = C-reactive protein
HMW = high molecular weight
IL = interleukin
LMW = low molecular weight
NF-κB = nuclear transcription factor kappa B
NO = nitric oxide
PPAR = peroxisome proliferator-activated receptor
TNF = tumor necrosis factor

located on chromosome 3q27 is expressed exclusively in adipose tissue, and recent genome-wide scans have mapped a diabetes susceptibility locus to this chromosome (8). The concentration of adiponectin circulating in plasma is very high (2 to 20 μg/ml) (9). Plasma levels of adiponectin in the Japanese population is about 5 to 10 μg/ml (10), and serum adiponectin is lower in Indo-Asians when compared with Caucasians (median 3.3 vs. 4.9 μg/ml) (11). Women have about 40% higher circulating levels of adiponectin than men (9).

Adiponectin exists in the circulation as a full-length protein and a putative proteolytic cleavage fragment consisting of the globular C-terminal domain. This globular domain of adiponectin is pharmacologically active and can regulate body weight and fatty acid oxidation in mice (12). Adiponectin is found in multiple oligomeric forms in serum, as a trimer and a hexamer (2 trimers) of lower molecular weight (LMW) form: LMW isoform and high molecular weight (HMW) forms: HMW isoform (13). The HMW form constitutes the major part of intracellular adiponectin, whereas the LMW form is predominant in the circulation. Levels of HMW isoform have better correlations with glucose tolerance than total adiponectin, suggesting that the HMW isoform of adiponectin is the active form (14). The LMW and HMW isoforms of adiponectin activate NF-κB (15). The HMW isoform of adiponectin is suppressed in coronary artery disease patients, and it is elevated on weight loss, and it suppresses human umbilical vein endothelial cell apoptosis (16).

Two adiponectin receptor forms have been cloned. AdipoR1 is a high-affinity receptor for the globular C-terminal domain of adiponectin with very low affinity for full-length adioponectin. AdipoR1 is abundantly expressed in skeletal muscle whereas AdipoR2 is most abundant in the liver where it has intermediate affinity for both forms of adiponectin (17). Overexpression or knock-down of AdipoR1/R2 suggests that these receptors mediate increased adenosine monophosphate (AMP) kinase and peroxisome proliferator-activated receptor (PPAR) ligands activities, as well as fatty-acid oxidation and glucose uptake by adioponectin (17). Adiponectin receptors are expressed in pancreatic β-cells (18), macrophages, and atherosclerotic lesions (19). Adiponectin receptor expression is increased by beta-cell exposure to the unsaturated free fatty acid oleate, and treatment of insulin-producing cells with globular adiponectin induces lipoprotein lipase expression (18).

Adiponectin itself is controlled in conditions of metabolic stress and by a number of hormones and factors involved in regulation of metabolic function. Insulin lowers adiponectin expression in both mice and humans (20). Thiazolidinediones, as potent PPARγ agonists, increase the expression of adiponectin (20,21). Most other factors with a significant impact on adiponectin regulation have inhibitory effects. These include catecholamines, glucocorticoids, cytokines (IL-6 and TNF-α), prolactin, growth hormone, and androgens (22).

Antiatherogenic Effects of Adiponectin

Laboratory data. ADIPONECTIN AND ENDOTHELIAL CELLS. Adiponectin reduces expression of adhesion molecules in endothelial cells and decreases cytokine production from macrophages by inhibiting NF-κB signaling through cAMP-dependent pathway (Fig. 1, Table 1) (23,24). At physiological levels, adiponectin exhibits specific and saturable binding to aortic endothelial cells and readily binds to the walls of catheter-injured vessels more than to intact vascular walls (25). Endothelium-dependent vasodilation in response to acetylcholine is significantly reduced in adiponectin-knockout mice when compared with wild-type mice (26).

ADIPONECTIN AND MONOCYTE-MACROPHAGES, FOAM CELL TRANSFORMATION. Adiponectin suppresses macrophage to foam cell transformation and prevents vascular stenosis. Adiponectin induces production of anti-inflammatory mediators IL-10 and -1 receptor antagonist (27). Expression of the scavenger receptor class A-1 of macrophages is inhibited by adiponectin, resulting in markedly decreased uptake of oxidized low-density lipoprotein and inhibition of foam cell formation (25). Adiponectin has inhibitory effects on the proliferation of myelomonocytic lineage cells and on the function of matured macrophages (28). Interleukin-6 treatment inhibits adiponectin gene expression and secretion in 3T3-L1 adipocytes (29). Adiponectin and TNF-α mutually inhibit each other's production in adipose tissue, and physiological concentrations of adiponectin inhibit TNF-α–induced monocyte adhesion to human aortic endothelial cells, as well as the expression of various adhesion molecules (Fig. 1) (23). In addition, adiponectin selectively increases tissue inhibitor of metalloproteinase-1 expression in human monocyte-derived macrophages through IL-10 induction (30).

ADIPONECTIN AND SMOOTH MUSCLE CELLS. Adiponectin suppresses the proliferation and migration of smooth muscle cells induced by platelet-derived growth factor in smooth muscle cells (31). Increasing adiponectin levels using an adenoviral vector attenuates neointimal proliferation in mechanically balloon injured arteries in adiponectin-deficient mice (32).

ADIPONECTIN AND INFLAMMATORY MARKERS. Plasma C-reactive protein (CRP) levels are negatively correlated with plasma adiponectin levels in male patients with coronary artery disease, and CRP messenger ribonucleic acid is

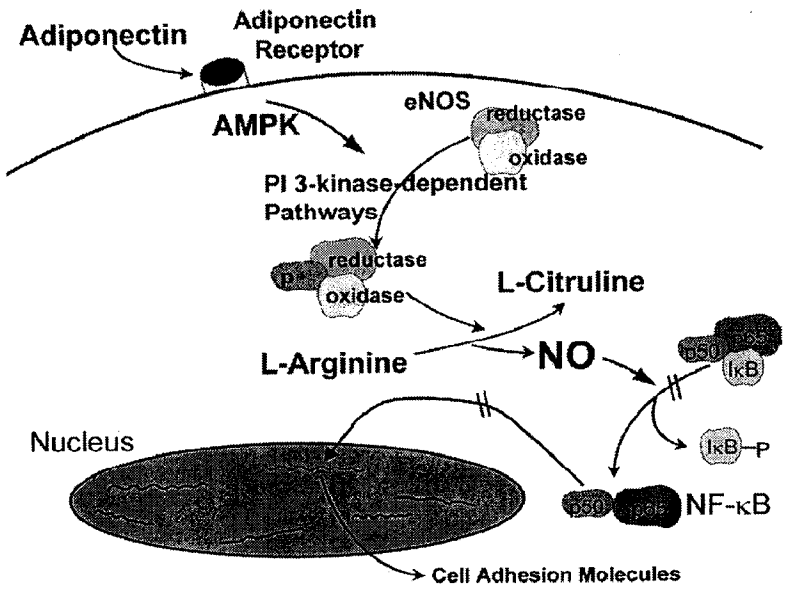

Figure 1 **Antiatherogenic Effects of Adiponectin**

Adiponectin has novel vascular actions to directly stimulate production of nitric oxide (NO) in endothelial cells using phosphatidylinositol (PI) 3-kinase-dependent pathways involving phosphorylation of endothelial nitric oxide synthase (eNOS) by adenosine-monophosphate-activated protein kinase (AMPK) (7) and reduces expression of adhesion molecules and decreases cytokine production from macrophage by inhibiting nuclear transcription factor kappa B (NF-κB) signaling through cyclic adenosine-monophosphate-dependent pathways (23,24). Modified from Koh KK, Han SH, Quon MJ. Inflammatory markers and the metabolic syndrome: insights from therapeutic interventions. J Am Coll Cardiol 2005;46:1978–85. IκB = inhibitory kappa B.

expressed in human adipose tissue. Of interest, a significant inverse correlation is observed between CRP and adiponectin messenger ribonucleic acid levels in human adipose tissues (33). Recent studies report an inverse correlation between plasma adiponectin and IL-6 concentrations (34). Thus, adiponectin may indirectly inhibit CRP and IL-6 expression through its ability to inhibit production of TNF-α.

Results from clinical surveys. Decreased plasma adiponectin levels are observed in patients with obesity, type 2 diabetes, hypertension, metabolic syndrome, and coronary artery disease (4,5,23,35,36). Low plasma adiponectin levels are significantly correlated with endothelial dysfunction (26). These results suggest that low adiponectin levels may be a useful marker for early-stage atherosclerosis. Hypoadiponectinemia correlates significantly and independently with coronary artery disease (4). Plasma concentrations of adiponectin in patients with acute coronary syndrome are significantly lower than those in patients with stable angina and in the control group (37). In addition, low plasma adiponectin levels are associated with progression of coronary artery calcification in type 1 diabetic and non-diabetic subjects independently of other cardiovascular risk factors (38). Plasma adiponectin levels are an inverse predictor of cardiovascular outcome in patients with end-stage renal disease and stroke (39–41).

Results from population surveys. Adiponectin levels in male subjects were measured at baseline and then followed for 6 years. Individuals with adiponectin concentrations in the highest quintile compared with the lowest quintile have a decreased risk for myocardial infarction (42). In addition, adiponectin is associated with a decreased risk for coronary heart disease events in same cohort, men with diabetes (43). However, adiponectin did not predict coronary heart disease events in women (44). Therefore, additional prospective studies are required to determine whether there is a true gender difference in the effect of adiponectin on coronary heart disease.

Effects of Adiponectin to Mimic and Augment Metabolic Actions of Insulin

Laboratory data. Activation of AMP kinase by adiponectin leads to expression of PPARα and induces increased gene expression of enzymes of fatty acid oxidation and glucose uptake (45). Adiponectin decreases hepatic glucose production by inhibiting enzymes of gluconeogenesis, and thus contributes to reduction in blood glucose levels in normal and diabetic animals (46). Of interest, administration of adiponectin improves insulin sensitivity in adiponectin-deficient mice made insulin resistant on a high-fat diet (47). Insulin, glucocorticoids, thyroid hormones, and growth hormone impair glucose tolerance, and/or contribute to insulin resistance. Among these hormones, only insulin and glucocorticoids suppress expression of adiponectin in adipocytes (48).

A number of genetic studies have demonstrated clear associations of polymorphisms and resulting in hypoadiponectinemia with insulin resistance, diabetes, and cardio-

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Table 1 Antiatherogenic and Anti-Insulin–Resistant Properties of Adiponectin and Inhibitors of Adiponectin Expression

Antiatherogenic Properties of Adiponectin	References
Stimulates production of NO	7
Suppresses human umbilical vein endothelial cells apoptosis	16
Reduces expression of adhesion molecules in endothelial cells	23
Decreases cytokine production from macrophages	24
Improves endothelium-dependent vasodilation	26
Induces production of IL-10 and -1 receptor antagonists	27
Suppresses macrophage-to-foam cell transformation	25
Inhibits expression of scavenger receptor class A-1 of macrophages	25
Inhibits proliferation of myelomonocytes and function of mature macrophages	28
Increases tissue inhibitor of metalloproteinase-1 expression in human monocyte-derived macrophages	30
Suppresses proliferation and migration of smooth muscle cells	31
Suppresses expression of growth factor in endothelial cells	32
Anti-Insulin–Resistant Properties of Adiponectin	
Ameliorates insulin resistance and increases fatty acid oxidation	12,45,47
Decreases hepatic glucose production by inhibiting enzymes of gluconeogenesis	46
Inhibitors of Adiponectin Expression	
TNF-α inhibits adiponectin production in adipose tissue	23
IL-6 inhibits adiponectin gene expression and secretion in 3T3-L1 adipocytes	29
CRP inhibits adiponectin mRNA levels in human adipose tissues	33
Insulin suppresess gene expression of adiponectin in adipocytes	20,48
Glucocorticoids suppress gene expression of adiponectin in adipocytes	48
Beta-adrenergic agonists inhibit gene expression of adiponectin	56
Hydrogen peroxide and nicotine reduce expression and secretion of adiponectin	56

CRP = C-reactive protein; IL = interleukin; mRNA = messenger ribonucleic acid; NO = nitric oxide; TNF = tumor necrosis factor.

vascular disease (8,49). These genetic factors may be relevant to effects of treatment with PPARγ agonists (50).

Evidence from clinical studies. Low adiponectin levels are associated with the metabolic syndrome and development of type 2 diabetes (5,51). Serum concentrations of adiponectin correlated strongly with insulin sensitivity in human (52). Subjects with type 2 diabetes have lower plasma concentrations of adiponectin than matched non-diabetic control subjects (36).

Effects of Therapeutic Interventions

Lifestyle modifications. Prolonged weight loss restores adiponectin levels (36) (Table 2). The HMW isoform of adiponectin is significantly increased, and levels of trimer and hexamer decline during weight loss (16).

Combined hypocaloric diet and moderate physical activity induce significant weight loss and increase of plasma adiponectin especially among diabetic subjects (53). After 2 years of weight loss and lifestyle changes, adiponectin levels increase significantly (54). Plasma levels of adiponectin are negatively associated with smoking status in patients with coronary artery disease (55). Increasing activity of the sympathetic nervous system, which is affected by nicotine, also decreases plasma levels of adiponectin. Moreover, β-adrenergic agonists and cyclic AMP analogues inhibit the gene expression of adiponectin (56). Consistent with this, adiponectin levels are significantly lower in current smokers than in non-smokers. In cultured mouse 3T3-L1 adipocytes, hydrogen peroxide and nicotine reduce messenger ribonucleic acid expression and secretion of adiponectin in a dose-dependent manner (57).

Cardiovascular drugs. RENIN-ANGIOTENSIN SYSTEM BLOCKING AGENTS. Renin-angiotensin system blocking agents significantly increase adiponectin levels with accompanying improvement in insulin sensitivity without affecting the degree of adiposity (58). Losartan alone or combined therapy with simvastatin and losartan in hypercholesterolemic, hypertensive patients significantly increases plasma adiponectin levels and insulin sensitivity relative to baseline measurements, but simvastatin alone therapy does not (59). Ramipril alone or combined therapy with simvastatin and ramipril in patients with type 2 diabetes shows the same

Table 2 Therapeutic Interventions on Raising Adiponectin Levels

Lifestyle Modifications	References
Weight loss restores adiponectin levels	16,36
Combined diet control and physical exercise increases plasma levels of adiponectin	53,54
Smoking habit decreases plasma adiponectin concentration	55,57
Increasing activity of the sympathetic nervous system decreases plasma levels of adiponectin	56
Renin-Angiotensin System Blocking Agents	
Temocapril and ramipril increase adiponectin levels	60
Losartan and candesartan increase adiponectin levels	58,59,63,67
PPARα Agonists	
PPARα agonist induces AdipoR2 on human primary macrophage	19
Fenofibrate increases adiponectin levels	19,65,67,68
PPARγ Agonists	
Thiazolidinediones induces expression and secretion of adiponectin in humans and rodents in vivo and in vitro	21
Thiazolidinediones increase adiponectin levels in diabetic, lean control, and obese control subjects	69
Hypoglycemic Drugs	
Glimepiride increases plasma adiponcetin levels in elderly patients with type 2 diabetes	70
Metformin does not alter plasma adiponectin levels in obese patients with type 2 diabetes	71
Statins	
Simvastatin, atorvastatin, and rosuvastatin do not change plasma levels of adiponectin	59,68,77
New Beta-Blockers	
Nebivolol increases plasma adiponcetin levels in hypertensive patients	79

PPAR = peroxisome proliferator-activated receptor.

results (60). Potential mechanisms for renin angiotensin system blocking agents to affect adiponectin levels include direct effects on glucose insulin-stimulated glucose uptake, promotion of adipogenic differentiation of preadipocytes (61), and/or induction of PPARγ activity promoting differentiation in adipocytes (62). Recent clinical trials demonstrate that renin-angiotensin system blockades lower the risk of development of type 2 diabetes. One of the mechanisms underlying this effect may be an increase in adiponectin levels and insulin sensitivity (63).

PPARα AGONISTS. The PPARα activators improve insulin sensitivity and reduce adiposity in rodent models (64). AdipoR2 is induced by both PPARα and PPARγ (19). Fenofibrate therapy significantly increases plasma adiponectin levels and insulin sensitivity in primary hypertriglyceridemic patients (65). Significant correlations between the degree of changes in adiponectin levels and insulin levels, CRP levels, and insulin sensitivity (assessed by Quantitative Insulin-Sensitivity Check Index [QUICKI]) were observed after fenofibrate therapy. Fenofibrate therapy for 2 months treatment increases adiponectin levels without a change in body weight. This raises the possibility that drug therapy is directly altering adiponectin levels independent of adiposity (66). We also investigated the effects of fenofibrate, candesartan, and combined therapy in hypertriglyceridemic, hypertensive patients. Fenofibrate, combined therapy, and candesartan significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements (67). In another study, fenofibrate alone or combined therapy with atorvastatin and fenofibrate for 2 months in patients with combined hyperlipidemia significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements, but atorvastatin alone therapy does not (68).

PPARγ AGONISTS. Thiazolidinediones induce expression and secretion of adiponectin in humans and rodents in vivo and in vitro without affecting body weight (21). Adiponectine levels rise uniformly in diabetic, lean control and obese control subjects after thiazolidinedione treatment (69). Glimepiride not only improves insulin resistance but also increases plasma adiponectin levels in elderly patients with type 2 diabetes (70). By contrast, metformin does not alter plasma adiponectin levels or adiponectin content in abdominal adipocytes even though glycemic control is similar in both troglitazone and metformin groups in obese patients with type 2 diabetes (71).

STATINS, BETA-BLOCKERS, AND DIURETICS. The effects of statins on insulin sensitivity are controversial. Simvastatin and atorvastatin improve insulin sensitivity in diabetic patients (72); however, others have reported that simvastatin either did not change or worsened insulin sensitivity in diabetic patients (73,74). Indeed, recent large-scale clinical studies have demonstrated that statins, particularly high dose, may increase, not decrease, the onset of new diabetes (75,76). Simvastatin, atorvastatin, or rosuvastatin does not change plasma levels of adiponectin and insulin sensitivity (59,68,77). Old beta-blockers and diuretics seem to have negative effects on insulin sensitivity (78). Nevertheless, new beta-blockers increase plasma adiponectin levels and improve insulin sensitivity (79).

Future Prospects

Adiponectin is a target for future research in reducing morbidity and mortality of atherosclerotic disease. Diet, exercise, cardiovascular drugs, and insulin sensitizers improve endothelium-dependent vascular function, increase adiponectin levels, and reduce inflammation and insulin resistance by distinct mechanisms (Fig. 2). This may help explain beneficial effects of combination therapies in recent clinical trials. Thus, there is a scientific rationale for recommending a combination of lifestyle modifications and multiple drugs from separate classes to prevent atherosclerosis and coronary heart disease. Recent evidence suggests that cross-talk between inflammatory signaling pathways and insulin signaling pathways causes both metabolic insulin resistance and endothelial dysfunction that synergize to predispose to cardiovascular disorders in the metabolic syndrome (Fig. 3) (3,80). Prospective studies are needed to examine the ability of increases in adiponectin levels and insulin sensitivity to improve primary end points including incidence of diabetes and outcomes of cardiovascular events. It is possible that recombinant adiponectin may have a beneficial therapeutic role in the treatment and prevention of cardiovascular diseases in the future.

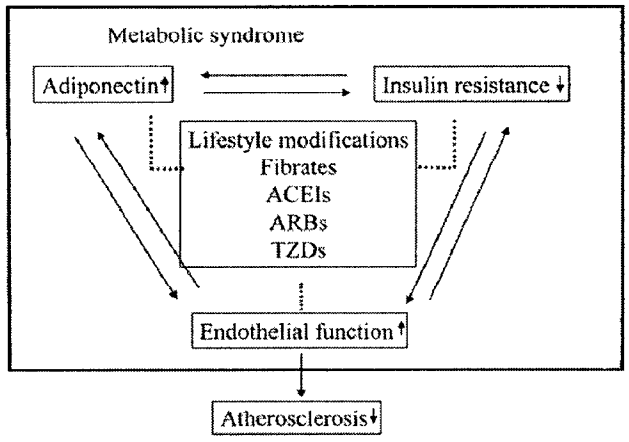

Figure 2 **Mechanisms of Therapeutic Interventions on Adiponectin, Insulin Resistance, and Endothelial Function**

Lifestyle modifications and cardiovascular drugs such as fenofibrate, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II type I receptor blockers (ARBs), and thiazolidinediones (TZDs) increase plasma levels of adiponectin, reduce insulin resistance, and improve endothelial function. These may be one mechanism to reduce cardiovascular diseases by these therapeutic interventions used in recent clinical trials.

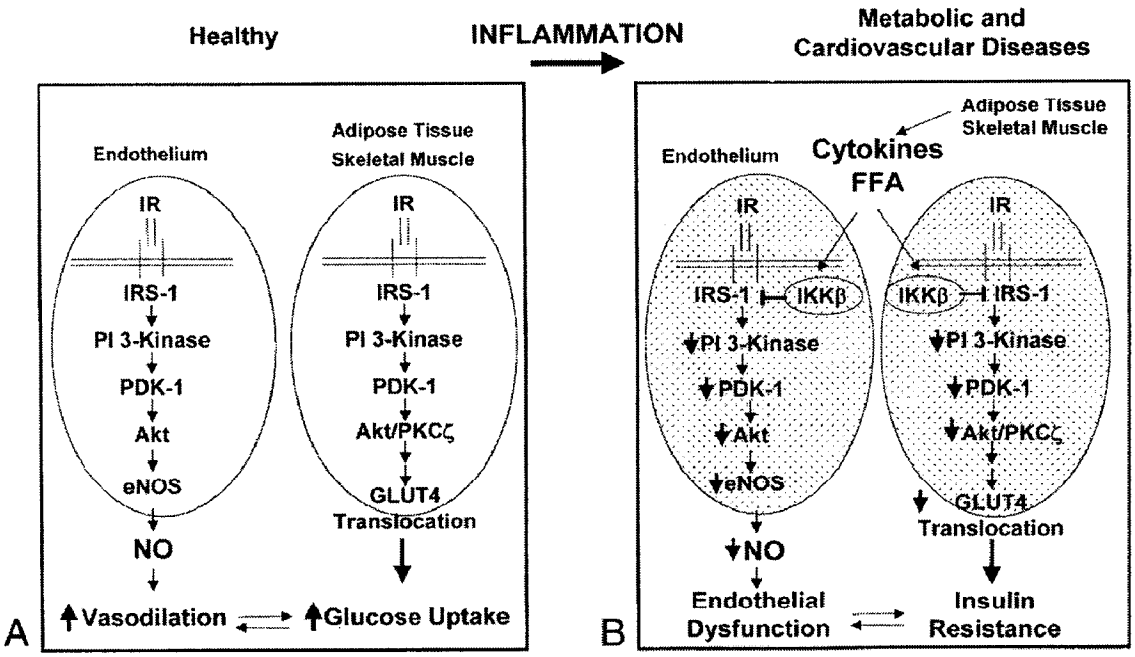

Figure 3 **Reciprocal Relationships Between Vascular and Metabolic Actions of Insulin in Health and Disease**

(A) Parallel phosphatidylinositol (PI) 3-kinase-dependent insulin signaling pathways in metabolic and vascular tissues synergistically couples metabolic and vascular physiology under healthy conditions. **(B)** Parallel impairment in insulin signaling pathways under pathological conditions contributes to synergistic coupling of insulin resistance (IR) and endothelial dysfunction (80). eNOS = endothelial nitric oxide synthase; FFA = free fatty acid; IKKβ = inhibitor of nuclear factor kappa B kinase beta; IRS = insulin receptor substrate; NO = nitric oxide; PDK = phosphoinositide-dependent kinase; PKCζ = protein kinase C zeta.

Reprint requests and correspondence: Dr. Kwang Kon Koh, Vascular Medicine and Atherosclerosis Unit, Division of Cardiology, Gil Heart Center, Gachon Medical School, 1198 Kuwoldong, Namdong-gu, Incheon, South Korea 405-760. E-mail: kwangk@gilhospital.com.

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